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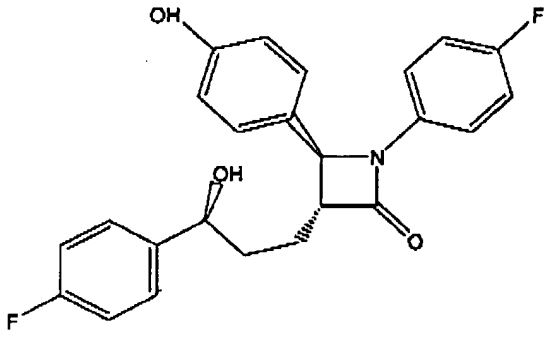
Response Under 37 CFR 1.116
Expedited Procedure
Examining Group 1617
Application No. 10/056,680
Amendment Dated: January 9, 2007
Reply to Final Office Action of July 11, 2006

REMARKS

Claims 1, 35-37, 42, 45 and 47 are pending in this application. Claims 4-10, 12-17, 21-34, 38-41, 46 and 48 have been withdrawn by the Examiner in the Office Action of January 29, 2004. Claims 2, 3, 11, 18-20, 43, and 44 were canceled, without prejudice to filing of one or more divisional or continuation applications directed to the canceled subject matter. Claims 1 and 47 were amended, not for reasons of prior art, but to expedite prosecution of the present application, without prejudice to the filing of one or more divisional or continuation applications directed to the amended subject matter. Claims 1 and 47, as amended, recite a composition and therapeutic combination, respectively, comprising 0.1 to 1000 milligrams of a sterol absorption inhibitor of Formula II shown above (ezetimibe) or pharmaceutically acceptable salts or solvates thereof; and 1 to 1000 milligrams of aspirin. These amendments are supported by original claims 3, 43 and 44 and in the specification at page 14, lines 12-28 and page 54, lines 22-27. No new matter has been added to the application by any of the foregoing amendments.

In embodiments set forth in claims 1 and 47, Applicants have discovered compositions and combinations comprising:

(a) 0.1 to 1000 milligrams of a sterol absorption represented by Formula (II):



(II)

or pharmaceutically acceptable salts or solvates thereof; and

(b) 1 to 1000 milligrams of aspirin.

See original claims 2, 3 and 20, page 14, lines 12-28, page 15, line 23 - page 17, line 4, and page 54, lines 22-27 of the specification.

In the Office Action of August 27, 2003, Applicants were required to elect a species of sterol absorption inhibitor, blood modifier, and third therapeutic agent. Applicants provisionally elected with traverse ezetimibe, which is represented by Formula (II) above.

Ezetimibe is the active ingredient in ZETIA® pharmaceutical formulation, which is commercially available from MSP (Merck Schering-Plough) Pharmaceuticals, Inc. See Response to Restriction Requirement and Election of Species of September 9, 2003 ("Response"). Ezetimibe is also one of the active ingredients in VYTORIN® ezetimibe/simvastatin pharmaceutical formulation, which is commercially available from MSP Pharmaceuticals, Inc.

In the same Response, Applicants provisionally elected with traverse aspirin as the blood modifier and simvastatin (an HMG CoA reductase inhibitor) as the third therapeutic agent.

The claimed compositions, combinations and treatment methods can be useful for treating vascular conditions and/or lowering concentration of a sterol in plasma in a mammal (page 72, lines 13-18 of the specification).

Applicants submit herewith for consideration the Declaration of Harry Davis, Jr., Ph.D. ("Davis Declaration"). Dr. Davis has a Bachelor of Science in Animal and Veterinary Science degree from the University of Maine (1977), Master of Science in Anatomical Pathology degree from George Washington University (1979) and a Doctorate Degree in Pathology from the University of Chicago (1982). Davis Declaration at paragraphs 1-3.

Dr. Davis is employed by Schering-Plough Research Institute ("Schering") as a Distinguished Research Fellow in the field of Cardiovascular and Metabolic Disease and has been employed in this capacity since 1993 and was previously employed by Schering

as a Principal Scientist since November 1987. Davis Declaration at paragraph 4. Dr. Davis' duties at Schering have included pharmaceutical drug discovery and basic research in lipid absorption and metabolism and metabolic disease. Davis Declaration at paragraph 5.

As discussed in Dr. Davis' Declaration, hypercholesterolemia has been associated with an increased sensitivity for platelets to aggregate and cause vascular complications. Davis Declaration at paragraph 6. A study was conducted under Dr. Davis' supervision to determine if a reduction in plasma cholesterol levels by ezetimibe (EZ) would enhance the ability of aspirin (ASA) to act as a platelet aggregation inhibitor. Davis Declaration at paragraph 6.

Rats were fed a 1% cholesterol + 0.5% cholate diet (HC) alone or containing ezetimibe (0.0036%, 3 mg/kg/day) for 7 days. Davis Declaration at paragraph 6. On day 7 they were treated with aspirin at 100 mg/kg or vehicle, and platelet aggregation determined. Davis Declaration at paragraph 6. Mean plasma cholesterol levels were reduced from 344 ± 22 mg/dl to 60 ± 4 mg/dl by ezetimibe treatment. Davis Declaration at paragraph 6. Platelet aggregation by adenosine diphosphate (ADP) and collagen was not altered, as expected, among the groups. Davis Declaration at paragraph 6. Arachidonic acid (AA) induced platelet aggregation at 0.3 mM was increased by the hypercholesterolemic diet compared to normal chow fed rats (Table), indicating an increased sensitivity to aggregate with hypercholesterolemia. Davis Declaration at paragraph 6. AA induced aggregation was not reduced in the aspirin alone treated hypercholesterolemic animals. Davis Declaration at paragraph 6. **AA induced aggregation was significantly reduced in the aspirin + ezetimibe treated rats compared to the aspirin alone treated hypercholesterolemic rats** (Table) (emphasis added). Davis Declaration at paragraph 6.

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Table: Platelet Aggregation

Agonist	Regular Chow	High Cholesterol (HC) diet	HC + EZ	HC + ASA (100 mpk)	HC + EZ + ASA (100 mpk)
AA (0.3 mM)	7 ± 3	14 ± 2	13 ± 2	12 ± 2	7 ± 2
AA (1 mM)	16 ± 2	17 ± 3	16 ± 3	14 ± 2	5 ± 2
ADP (10 μM)	24 ±1	21 ± 2	21 ± 3	25 ± 2	31 ± 1
Collagen (3 μg/ml)	25 ± 1	24 ± 3	27 ± 3	30 ± 2	32 ± 1

Aggregation in whole blood (ohms)
N=6 per group, Mean ± SEM

In Dr. Davis' opinion, these results indicate that the combination of ezetimibe with aspirin synergistically and unexpectedly enhances the ability of aspirin to inhibit platelet aggregation, and combination of ezetimibe and aspirin will prevent vascular complications greater than either agent alone. Davis Declaration at paragraph 6. *The above test data provide evidence of unexpected synergy of the combination of ezetimibe and aspirin to inhibit platelet aggregation when compared to treatment with aspirin alone or ezetimibe alone.*

Also, Applicants submit herewith for consideration the Declaration of Madhu Chintala, Ph.D. ("Chintala Declaration"). Dr. Chintala has a Bachelor of Science degree in Zoology from the University of Madras, India (1984), Master of Science degree in Ocean Life Sciences from the University of Madras, India (1985) and a Doctorate Degree in Pharmacology from the University of Houston (1991). Chintala Declaration at paragraphs 1-3.

Dr Chintala has been employed by Schering-Plough Research Institute ("Schering") as an Associate Director in the field of Cardiovascular and Metabolic Disease since 2003 and was previously employed by Schering as a scientist since 1991.

Chintala Declaration at paragraph 4. Dr. Chintala's duties at Schering have included pharmaceutical drug discovery and basic research in the areas of atherothrombosis, heart failure, lipid disorders and metabolic diseases. Chintala Declaration at paragraph 5.

The above platelet aggregation study was also conducted under the supervision of Dr. Chintala. Chintala Declaration at paragraph 6.

The Examiner requested information on dosing for humans vs. rats. Final Office Action at pages 5-6. In his Declaration, Dr. Chintala discussed the rationale for dose selection of aspirin and ezetimibe for the above study in rats, as follows. Chintala Declaration at paragraphs 7-9. Aspirin is an antiplatelet agent which is widely used to prevent atherothrombosis in the treatment of cardiovascular disorders including stroke. Chintala Declaration at paragraph 7. Aspirin exerts its beneficial effects by inhibiting platelet aggregation and thrombus formation also commonly referred to as blood clots. Chintala Declaration at paragraph 7. Ex-vivo platelet aggregation (a measure of platelet function) has widely been used as a surrogate for antithrombotic activity and for determining the therapeutic doses of aspirin in humans and in animals. Chintala Declaration at paragraph 7.

The dose of aspirin used clinically to treat patients varies depending on the indication/disease conditions. Chintala Declaration at paragraph 7. A standard dose of 100 mg/day was shown sufficient to inhibit platelet aggregation in 90% of patients in primary and secondary prevention of cardiovascular diseases.[1] Chintala Declaration at paragraph 7. Doses of 300 and 600 mg/day were required in stroke patients with single or recurring events.[2] Chintala Declaration at paragraph 7. Higher doses of 500-1000 mg were found effective in the treatment of fever and other symptoms of upper respiratory tract infection in adults[3], in the treatment of episodic tension-type headache[4], and to

[1] Syrbe et al., *Individual Dosing of ASA Prophylaxis by Controlling Platelet Aggregation*, Clin. Appl. Thromb. Hemost. Jul; 7(3): 209-13, 2001 (Abstract only).
[2] Chamorro et al., *Ex Vivo Response to Aspirin Differs in Stroke Patients with Single or Recurrent Events: A Pilot Study*, J. Neurol. Sci. Dec 15; 171(2); 110-4, 1999.
[3] Bachert et al., *Aspirin Compared with Acetaminophen in the Treatment of Fever and Other Symptoms of Upper Respiratory Tract Infection in Adults: A Multicenter, Randomized, Double-Blind, Double-Dummy,*

prevent platelet activation in patients before and after percutaneous coronary interventions[5]. Chintala Declaration at paragraph 7. In Dr. Chintala's opinion, the dose of aspirin varies in humans depending on the clinical indication and it is reasonable to assume that the therapeutic range is from 1-1000 mg. Chintala Declaration at paragraph 7.

In the above rat studies, Dr. Chintala used aspirin at 100 mg/kg, orally. Chintala Declaration at paragraph 8. In Dr. Chintala's experience, this dose of aspirin is necessary to inhibit platelet aggregation in rats 1-2 hrs after oral dosing. Chintala Declaration at paragraph 8. Studies in the literature have employed different doses of aspirin in rats and the dose varies upon the route of administration and the type of injury/thrombosis model used. Chintala Declaration at paragraph 8. In a rat model of laser-induced thrombosis, administration of aspirin at 100 mg/kg prevented thrombus formation.[6] Chintala Declaration at paragraph 8. In a similar laser-injury model, Vesvres et al, 1993, have shown that doses of 50, 100 and 200 mg/kg, administered intramuscularly prevented thrombus formation in a dose dependent manner.[7] Chintala Declaration at paragraph 8. Killackey et al, 1984, have reported that they required 200 mg/kg of aspirin to prevent carotid artery thrombosis in a rat model and that the 100 mg/kg dose was insufficient.[8] Chintala Declaration at paragraph 8. In contrast, several reports have shown that doses of aspirin ranging from 1-50 mg/kg did not significantly inhibit thrombus formation in rats[9,10] or they had modest effects.[11,12] Chintala Declaration at paragraph 8. Thus, the

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Placebo-Controlled, Parallel-Group, Single-Dose, 6-Hour Dose-Ranging Study, Clin. Ther. Jul; 27 (7): 993-1003, 2005.

[4] Steiner et al., *Aspirin in Episodic Tension-Type Headache: Placebo-Controlled Dose-Ranging Comparison with Paracetamol*, Cephalalgia, Feb; 23 (1): 59-66, 2003.

[5] ten Berg et al., *High-Dose Aspirin in Addition to Daily Low-Dose Aspirin Decreases Platelet Activation in Patients Before and After Percutaneous Coronary Intervention*, Thromb. Res. Mar; 105 (5): 385-90.

[6] Aguejouf et al., *Effects of Acetyl Salicylic Acid Therapy on an Experimental Thrombosis Induced by Laser Beam*, Thromb. Res. Sep 15; 99(6): 595-602, 2000.

[7] Vesvres et al., *Effects of Aspirin on Embolization in an Arterial Model of Laser-Induced Thrombus Formation*, Haemostasis. 23(1): 8-12, 1993 (Abstract ony).

[8] Killackey et al., *The Effects of High Doses of Aspirin and Related Benzoic Acid Derivatives on Arterial Thrombosis in Male Rats*, Haemostasis. 14(4): 354-60, 1984 (Abstract only).

[9] Schumacher et al., *Superior Activity of a Thromboxane Receptor Antagonist as Compared with Aspirin in Rat Models of Arterial and Venous Thrombosis*, J Cardiovasc Pharmacol. Oct; 22(4): 526-33, 1993.

therapeutic dose of aspirin in rats is around 100 mg/kg. Chintala Declaration at paragraph 8. Therefore, in Dr. Chintala's opinion, the dose used in the above studies in the therapeutic range for prevention of thrombosis in rats is consistent with reports in the literature. Chintala Declaration at paragraph 8. While on an mg/kg basis, the dose of aspirin used in the above studies (100 mg/kg in rats) is much higher than the 1-1000 mg/day (total dose) in humans, it is still in the therapeutic range for rats. Chintala Declaration at paragraph 8. The reason for the difference in dose from rats to humans can be due to multiple factors influenced by the absorption, metabolism and elimination of the aspirin, and is not clearly understood. Chintala Declaration at paragraph 8.

In the above study, rats were dosed with ezetimibe at 3 mg/kg/day, which was previously found to be the maximally effective dose to prevent diet-induced hypercholesterolemia in rats.[13] Chintala Declaration at paragraph 9. Therefore, in Dr. Chintala's opinion, doses ranging from 0.1-1000 mg of ezetimibe/day, with the usual dose of 10 mg of ezetimibe/day, should be effective clinically in humans. Chintala Declaration at paragraph 9.

Copies of each of the literature references cited above are attached hereto as Exhibits 1-13.

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[10] Lockyer et al., *Demonstration of Flow and Platelet Dependency in a Ferric Chloride-Induced Model of Thrombosis*, Cardiovasc Pharmacol. May; 33(5): 718-25, 1999.
[11] Hirose et al., *Antiplatelet and Antithrombotic Effects of a Novel Selective Phosphodiesterase 3 Inhibitior, NSP-513, in Mice and Rats*, Japanese J Pharmacol. Mar; 82(3): 188-98, 2000 (Abstract only).
[12] Schumacher et al., *A Ferret Model of Electrical-Induction of Arterial Thrombosis That is Sensitive to Aspirin*, J Pharmacol Toxicol Methods. Feb; 35(1): 3-10, 1996.
[13] van Heek et al., *Ezetimibe Potently Inhibits Cholesterol Absorption But Does Not Affect Acute Hepatic or Intestinal Cholesterol Synthesis in Rats*, British Journal of Pharmacology 138: 1459-1464, 2003.

The Rejection

At pages 3-7 of the Final Office Action, claims 1, 3, 35-37, 42-45 and 47 were rejected under 35 U.S.C. § 103(a) over EP 0720599 ("Rosenblum et al.") and WO 99/47123 ("Ullah") in view of Frei (Proc. Soc. Exp. Biol. Med. 1999 Dec; 222(3): 196-204). Final Office Action at page 3.

In the Final Office Action, it was alleged, *inter alia*, that Rosenblum et al. disclose that compositions including the compound of Formula II can be combined with HMG CoA reductase inhibitors such as simvastatin to reduce cholesterol and risk of atherosclerosis. Final Office Action at page 3. Ullah was cited as teaching a composition comprising statins, such as simvastatin, in combination with aspirin, for cholesterol lowering and treating or reducing the risk of developing atherosclerosis. Final Office Action at pages 3-4. Ullah allegedly teaches an aspirin dosage of 50-650 mg. Final Office Action at page 3.

It is acknowledged in the Office Action that the primary references do not expressly teach the claimed composition comprising the compound of Formula II (ezetimibe), aspirin and simvastatin together or that antioxidants be incorporated into such as composition. Final Office Action at pages 3-4. It is alleged that Frei teaches that antioxidants such as vitamins C or E can be useful for inhibiting atherogenesis and normalizing vascular functions. Final Office Action at page 4.

In the Office Action, it is further alleged that it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the compound of Rosenblum et al. and that of Ullah, which are known to be useful to reduce cholesterol level and the risk of atherosclerosis individually, into a single composition useful for the very same purpose, citing *In re Kerkoven*, 205 U.S.P.Q. 1069. Final Office Action at page 4. Further, it is asserted that one of ordinary skill in the art would have been motivated to include an antioxidant since vitamin C, an antioxidant, is known to inhibit the development of atherosclerosis. Final Office Action at page 4.

In the Response to Arguments section of the Final Office Action, it is alleged that the Declaration of Dr. Davis is not clear as to whether the test results are unexpected.

Final Office Action at page 5. Also, it is asserted that the dosage of aspirin and ezetimibe resulting in unexpected benefits is not recited in the claims. Final Office Action at page 5.

The Prior Art

Rosenblum et al. disclose the compound of Formula II (ezetimibe) at page 29, Ex. 6. Rosenblum et al. disclose starch-based pharmaceutical compositions including compounds of Formula I of Rosenblum et al. (Ex. A and B Page 29). Rosenblum et al. teach that the active compounds therein can be combined with HMG CoA reductase inhibitors, such as simvastatin (Page 5, paragraph 0028). Rosenblum et al. also disclose that the active compounds are useful for reducing cholesterol and the risk of atherosclerosis (claims).

Ullah discloses the use of a combination of aspirin for reducing myocardial infarction and a statin (such as simvastatin) for lowering cholesterol and preventing or treating atherosclerosis at page 1, lines 14-18, in combination.

Frei discloses that antioxidants may inhibit atherogenesis and improve vascular function by two different mechanisms (Abstract). Lipid-soluble antioxidants present in LDL, such as vitamin C, can inhibit LDL oxidation (Abstract). Antioxidants present in the cells of the vascular wall decrease cellular production and release of reactive oxygen species (ROS), inhibit endothelial activation and improve the biologic activity of ENDO (Abstract).

The Required *Prima Facie* Case of Obviousness Under 35 U.S.C. § 103 Has Not Been Established

When making a rejection under 35 U.S.C. § 103, the Examiner has the burden of establishing a *prima facie* case of obviousness. In re Fritch, 972 F.2d 1260, 1265 (Fed. Cir. 1992). The Examiner can satisfy this burden only by showing an objective teaching in the state of the art, which would lead an individual to combine the relevant teachings

of the references [and/or the knowledge] in the manner suggested by the Examiner. Id.; In re Fine, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988).

The mere fact that the state of the art could be modified does not make the modification obvious unless the state of the art suggests the desirability of the modification. In re Fritch, 23 U.S.P.Q.2d at 1784; In re Laskowski, 10 U.S.P.Q.2d 1397, 1398 (Fed. Cir. 1989); In re Gordon, 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984).

"It is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious....'one cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.'" In re Fritch, 972 F.2d at 1266 (quoting In re Fine, 5 U.S.P.Q.2d at 1600).

"The ultimate determination of patentability must be based on consideration of the entire record, by a preponderance of evidence, **with due consideration to the persuasiveness of any arguments and any secondary evidence.**" Manual of Patent Examining Procedure, (Rev. 1, Feb. 2003) § 716.01(d) (emphasis added) and In re Oetiker, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992).

Claims 1, 18-20 and 47

Claims 1 and 47, as amended, recite a composition and therapeutic combination, respectively, comprising 0.1 to 1000 milligrams of a sterol absorption inhibitor of Formula II shown above (ezetimibe) or pharmaceutically acceptable salts or solvates thereof; and 1 to 1000 milligrams of aspirin.

It is respectfully submitted that the combination of the references cited as rendering the claimed invention obvious is improper because there is no suggestion in the cited references to combine the claimed components of ezetimibe and aspirin in the recited amounts.

Applicants wish to emphasize that claim 1 does not require the presence of an optional third component, such as a statin.

With respect to patentability of a composition or combination of a sterol absorption inhibitor and aspirin, Rosenblum does not suggest or disclose combinations of a sterol absorption inhibitor and blood modifier such as aspirin. Rosenblum does not suggest or disclose that the disclosed sterol absorption inhibitors have any effect on platelet aggregation.

Ullah does not suggest or disclose combinations of a sterol absorption inhibitor and blood modifier such as aspirin. Further, in Ullah, *aspirin is disclosed as being useful for reducing myocardial infarction* at page 1, lines 14-18, *not for treating atherosclerosis*. Ullah does not disclose sterol absorption inhibitors. The statin in Ullah is disclosed as lowering cholesterol and treating atherosclerosis. Id.

In the Final Office Action at pages 4 and 5, *In re Kerkoven* was cited as supporting the argument that combining the compositions of Rosenblum and Ullah, which are known to be useful to reduce cholesterol level and the risk of atherosclerosis individually, into a single composition useful for the very same purpose would be considered obvious.

However, Ullah does *not* disclose aspirin as being useful for lowering cholesterol or treating atherosclerosis, but rather for treating myocardial infarction. Therefore *In re Kerkoven* does not apply since Ullah does not disclose aspirin as having the same purpose as a cholesterol absorption inhibitor or HMG CoA reductase inhibitor, namely to lower cholesterol and thereby treat atherosclerosis.

Frei does not disclose sterol absorption inhibitors or blood modifiers such as aspirin.

Even if the teachings of Frei were combined with those of Rosenblum et al. and Ullah as suggested in the Final Office Action, one skilled in the art would not be motivated to provide a composition having a sterol absorption inhibitor and blood modifier such as aspirin in the recited amounts. *In re Kerkoven* does not apply since Ullah only discloses aspirin as useful for treating myocardial infarction and does not

disclose aspirin as having the same purpose as a cholesterol absorption inhibitor or HMG CoA reductase inhibitor, namely to lower cholesterol and thereby treat atherosclerosis.

Further, Applicants respectfully request consideration of the evidence set forth in the Davis and Chintala Declarations. These results indicate that the combination of ezetimibe with aspirin unexpectedly synergistically enhances the ability of aspirin to inhibit platelet aggregation, and combination of ezetimibe and aspirin will prevent vascular complications greater than either agent alone. Davis Declaration at paragraph 6. The above test data provide evidence of unexpected synergy of the combination of ezetimibe and aspirin to inhibit platelet aggregation when compared to treatment with aspirin alone or ezetimibe alone. None of the cited references, taken alone or combined as set forth in the rejection, suggests or discloses the unexpected synergy of the combination of ezetimibe and aspirin to inhibit platelet aggregation. Affidavits or declarations, when timely presented, containing evidence of criticality or unexpected results, commercial success, long-felt but unsolved needs, failure of others, skepticism of experts, etc., must be considered by the examiner in determining the issue of obviousness of claims for patentability under 35 U.S.C. 103. M.P.E.P. 716.01(a). The Court of Appeals for the Federal Circuit stated in *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538, 218 USPQ 871, 879 (Fed. Cir. 1983) that "evidence rising out of the so-called 'secondary considerations' must always when present be considered en route to a determination of obviousness." M.P.E.P. 716.01(a). Applicants respectfully request that these unexpected results be considered as evidence of non-obviousness in the determination of patentability.

Therefore, the *prima facie* case of obviousness based upon Rosenblum et al., Ullah and Frei has not been established and the rejection of claims 1, 18-20 and 47 should be reconsidered and withdrawn. If claims 1 and 47 are determined to be non-obvious, then claims 18-20, 35-37 and 42-45, which depend from claim 1, also should be determined to be non-obvious.

Claims 35-37

Claims 35-37 depend from claim 1 and further recite at least one HMG CoA reductase inhibitor, such as simvastatin. Thus the composition would comprise sterol absorption inhibitor, aspirin, and HMG CoA reductase inhibitor, such as simvastatin.

It is respectfully submitted that the combination of the references cited as rendering the claimed invention obvious is improper because there is no suggestion in the cited references to combine the claimed components of sterol absorption inhibitor (such as that of Formula (I) (e.g., ezetimibe)), aspirin, and HMG CoA reductase inhibitor.

As discussed above, Rosenblum et al. and Ullah provide no motivation for a triple combination of sterol absorption inhibitor, aspirin, and HMG CoA reductase inhibitor. *In re Kerkoven* does not apply since Ullah only discloses aspirin as useful for treating myocardial infarction and does not disclose aspirin as having the same purpose as a cholesterol absorption inhibitor or HMG CoA reductase inhibitor, namely to lower cholesterol and thereby treat atherosclerosis. Frei only discloses antioxidants as useful for treating atherosclerosis and therefore is not relevant to the rejection of these claims. Applicants respectfully request consideration of the evidence of unexpected results of the combination of ezetimibe and aspirin as set forth in the Davis and Chintala Declarations and as discussed above as evidence of non-obviousness in the determination of patentability.

Therefore, the *prima facie* case of obviousness based upon Rosenblum et al., Ullah and Frei has not been established and the rejection of claims 35-37 should be reconsidered and withdrawn.

Claims 42-45

Claims 42-45 depend from claim 1 and further recite at least one antioxidant or vitamin. Thus the composition would comprise sterol absorption inhibitor, aspirin, and antioxidant or vitamin.

Applicants wish to emphasize that claim 1 does not require the presence of a third component, such as a statin.

With respect to patentability of a composition or combination of a sterol absorption inhibitor, aspirin and antioxidant or vitamin (*without the presence of a statin*), Rosenblum does not suggest or disclose combinations of a sterol absorption inhibitor and blood modifier such as aspirin. Ullah does not suggest or disclose combinations of a sterol absorption inhibitor and blood modifier such as aspirin.

In Ullah, *aspirin is disclosed as being useful for reducing myocardial infarction* at page 1, lines 14-18, *not for treating atherosclerosis*. The statin in Ullah is disclosed as lowering cholesterol and treating atherosclerosis. Id.

In the Office Action, *In re Kerkoven* was cited as supporting the argument that combining the compositions of Rosenblum and Ullah, which are known to be useful to reduce cholesterol level and the risk of atherosclerosis individually, into a single composition useful for the very same purpose would be considered obvious.

However, the invention of claims 42-45 is for a sterol absorption inhibitor, aspirin and antioxidant or vitamin. Ullah does *not* disclose aspirin as being useful for lowering cholesterol or treating atherosclerosis. *In re Kerkoven* does not apply since Ullah only discloses aspirin as useful for treating myocardial infarction and does not disclose aspirin as having the same purpose as a cholesterol absorption inhibitor or HMG CoA reductase inhibitor, namely to lower cholesterol and thereby treat atherosclerosis.

Frei does not disclose sterol absorption inhibitors or blood modifiers such as aspirin. Even if the teachings of Frei were combined with those of Rosenblum et al. and Ullah as suggested in the Final Office Action, one skilled in the art would not be motivated to provide a composition having a having a sterol absorption inhibitor, blood modifier such as aspirin and vitamin or antioxidant.

Applicants respectfully request consideration of the evidence of unexpected results of the combination of ezetimibe and aspirin as set forth in the Davis and Chintala

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Declarations and as discussed above as evidence of non-obviousness in the determination of patentability.

Therefore, the *prima facie* case of obviousness based upon Rosenblum et al., Ullah and Frei has not been established and the rejection of claims 42-45 should be reconsidered and withdrawn.

Accordingly, Applicants respectfully request that the § 103(a) rejection of claims 1, 18-20, 35-37, 42-45 and 47 be reconsidered and withdrawn. Also, Applicants respectfully request rejoinder and allowance of claims 38-41 withdrawn by restriction, which were timely traversed, and claims 46 and 48.

Respectfully submitted,

Date: **January 9, 2007**

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